REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 11, 31-32, 34, 36-43, and 58), drawn to antibodies to the polypeptide of SEQ ID NO:1, compositions thereof, and methods of making the antibodies, is acknowledged.

Claims directed to methods of using the antibodies for detecting polypeptides specifically bound by the antibodies (i.e., claim 44) and for purifying polypeptides specifically bound by the antibodies (i.e., claim 45), could and should be examined together with the product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants presume that these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

II. Information disclosure statement

The Office Action indicates that "[t]he references on PTO 1449, filed 12/4/01 have been crossed out because none of the references have been submitted to the Office" (Office Action, August 13, 2002; page 3). This is improper. Copies of the references cited in the Information Disclosure Statement of December 4, 2001 are not necessary, according to 37 C.F.R. § 1.98(3)(d):

> (d) A copy of any patent, publication, pending U.S. application or other information . . . listed in an information disclosure statement is required to be provided, even if the patent, publication, pending U.S. application or other information was

previously submitted to, or cited by, the Office in an earlier application, unless:

(1) The earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C. 120; and

(2) The information disclosure statement submitted in the earlier application complies with paragraphs (a) through (c) of this section.

The Information Disclosure Statement filed with the instant application on December 4, 2001 discloses that "copies of the references are not included herein as copies were previously cited by or submitted to the Office in parent applications Serial No. 09/249,241, filed February 11, 1999, and Serial No. 09/019,216, filed February 5, 1998, from which we are claiming priority under 35 U.S.C. 120." The instant application claims priority to the parent applications (U.S. Serial No. 09/249,241 and U.S. Serial No. 09/019,216) as indicated, for example, on page 1 of the Specification, and on page 1 of the Transmittal Letter submitted with the instant application. Since the Information Disclosure Statement of December 4, 2001 meets the requirements of 37 § 1.98(3)(d), and since copies of the cited references were submitted to the Patent Office in the parent applications, it is not necessary to provided additional copies of the cited references in the instant application. Therefore, the Patent Office must consider the references cited in the Information Disclosure Statement of December 4, 2001.

III. Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 11, 31-32, 34, 36-43, and 58 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use antibodies which specifically bind to the recited "variants" and "fragments" of SEQ ID NO:1 (Office Action, August 13, 2002; pages 3-4). In particular, the Office Action has asserted that the specification "**does not** reasonably provide enablement for (1) *any* isolated antibody which specifically binds to (a) *any* polypeptide comprising *any* naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 wherein said polypeptide has CoA dehydrogenase activity, (b) *any* fragment of a polypeptide 'having' the amino acid sequence of SEQ ID NO:1, (c) *any* fragment 'comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO:1" (Office Action, page 3; emphasis in

original). Such, however, is not the case.

The specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., at page 28, line 6 to page 29, line 23; and page 51, lines 4-19). Given the information provided by SEQ ID NO:1 (the amino acid sequence of HSCD), one of skill in the art would be able to routinely obtain antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1," "a polypeptide comprising a fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1," and "a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1." For example, an animal could be immunized with any of the recited variants and fragments of SEQ ID NO:1, antibodies could be isolated from the animal, and the antibodies could be screened to identify antibodies which specifically bind to the polypeptide.

Likewise, the specification discloses methods to use antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence in, for example, the purification of such polypeptides (e.g., at page 51, line 21 to page 52, line 2), the detection and/or measurement of such polypeptides (e.g., at page 25, lines 4-11; and page 35, line 29 to page 36, line 17), and the competitive screening of drug candidates (e.g., at page 41, lines 20-23). Given the information provided by SEQ ID NO:1 (the amino acid sequence of HSCD), one of skill in the art would be able to routinely use antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1," "a polypeptide comprising a fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1," and "a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1." For example, an antibody which specifically binds to any of the recited variants and fragments of SEQ ID NO:1 could be coupled to an activated chromatographic resin, and this resin could then be used in an immunoaffinity column to purify the polypeptide.

In support of this rejection, the Office Action states that "there is insufficient guidance as to which undisclosed antibody would binds to *any* naturally occurring amino acid sequence at least 90%

identical (at least 10% difference) to the amino acid sequence of SEQ ID NO:1 with the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO:1" (Office Action, August 13, 2002; page 5). Furthermore, the Office Action asserts that "there is insufficient guidance as which undisclosed antibody (antibody binding specificity) would specifically binds to *any* fragment 'comprises at least *any* 15 contiguous amino acid sequence residues of SEQ ID NO:1" (Office Action, page 5). These assertions are incorrect. Firstly, the Office Action is incorrect in characterizing the claimed antibodies as "undisclosed." Variants of SEQ ID NO:1 are disclosed in the specification at, for example, page 3, lines 5-6; page 6, line 18 to page 7, line 4; page 7, lines 9-12; page 14, lines 12-19; and page 15, lines 15-18. Fragments of SEQ ID NO:1 are disclosed in the specification at, for example, page 3, lines 2-4; page 7, lines 5-9; page 8, lines 15-18; page 28, lines 21-25; and page 51, lines 7-16. Antibodies which specifically bind to HSCD, and variants and fragments thereof, are disclosed in the specification at, for example, page 4, lines 9-11; page 7, lines 21-29; and page 28, lines 6-12. Therefore, the claimed antibodies are fully disclosed in the specification.

Secondly, the Office Action is incorrect in requiring that the antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1 have the "same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO:1" (Office Action, August 13, 2002; page 5). The Patent Office has improperly interpreted the claims as reciting antibodies which are specific for "the full length polypeptide comprising SEQ ID NO:1." This is incorrect. The claimed antibodies are specific for the particular polypeptides, polypeptide variants, and/or polypeptide fragments to which they specifically bind. The Office Action attempts to support its position by citing Kuby et al. (1994; Immunology, Second edition, W.H. Freeman and Company, New York, NY, pages 86-96), which teaches that "immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues (fragment) or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide, let alone a polypeptide with 10% difference" (Office Action, August 13, 2002; pages 5-6; emphasis in original). However, this reference is irrelevant because there is no requirement that the claimed antibodies have the "same specificity as the antibody that binds to the full length polypeptide comprising

SEQ ID NO:1."

Thirdly, the Office Action is incorrect in asserting that there is "insufficient guidance" to the claimed antibodies. Antibodies which specifically bind to a polypeptide can be made as long as that polypeptide, or fragments thereof, are available; there is no restriction on the amino acid sequence of polypeptides that can be used to make antibodies. Since a polypeptide having **any** amino acid sequence (including any amino acid sequence that is 90% identical to SEQ ID NO:1, any naturally occurring amino acid sequence that is 90% identical to SEQ ID NO:1, and any fragment of SEQ ID NO:1) can be used to make antibodies using the methods disclosed in the specification, it is not necessary to identify particular naturally occurring amino acid sequences that are 90% identical to SEQ ID NO:1, or particular fragments of SEQ ID NO:1, that could be used in this manner.

The Office Action attempts to provide further support for this rejection by citing Ngo et al. (1994; in The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, pages 492-495), which teaches that "amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance" (Office Action, August 13, 2002; page 5). The Office Action has ignored the guidance provided by the claims themselves and the specification. For example, the claimed antibodies included antibodies which specifically bind to "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity." An assay to measure CoA dehydrogenase activity is disclosed in the specification at, for example, page 50, line 21 to page 51, line 2. One of ordinary skill in the art could routinely use the disclosed assay to identify polypeptide variants recited by the claims, and could routinely make and/or use antibodies which specifically bind to these polypeptide variants. Contrary to the Office Action's assertions, no undue experimentation would be required.

The Office Action also asserts that the use of the terms "having" and "comprising" "expands the polypeptide fragment to which the antibody binds to include additional amino acid residues at either or both ends" (Office Action, August 13, 2002; page 5). To the contrary, the claimed antibodies are fully

enabled by the specification.

Nevertheless, to expedite prosecution, claim 11 has been amended such that it recites antibodies which bind to an epitope of SEQ ID NO:1, which bind to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1, or which bind to an epitope of a fragment of a polypeptide consisting of SEQ ID NO:1. Support for these amendments can be found in the specification at, for example, page 8, lines 1-6. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include antibodies which bind to epitopes other than those recited in the claims. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claims, as amended, recite patentable subject matter.

The Office Action asserts that, with regard to compositions comprising the recited monoclonal and polyclonal antibodies, "the specification fails to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* specific disease using *any* antibody mentioned above" (Office Action, August 13, 2002; page 6). Methods to treat patients with the recited compositions are not recited in the claims. The claims at issue recite compositions comprising monoclonal and/or polyclonal antibodies. The recited compositions can be used, for example, to detect and/or purify polypeptides which are specifically bound by the recited antibodies. Therefore, the claimed compositions are fully enabled, and no guidance "with respect to treating a patient" is necessary.

Furthermore, the Office Action asserts that, with respect to chimeric antibodies, "[i]n the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other function properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use" (Office Action, August 13, 2002; page 6). Methods to treat patients with the recited chimeric antibodies are not recited in the claims. The claims at issue recite chimeric antibodies which specifically bind to polypeptides of SEQ ID NO:1. The recited chimeric antibodies can be used, for example, to detect and/or purify polypeptides which are

specifically bound by the recited antibodies. Therefore, the claimed chimeric antibodies are fully enabled, and no guidance "for *in vivo* therapeutic use" is necessary.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present specification would enable one to make and use the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection is requested.

IV. Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 11, 31-32, 34, 36-43, and 58 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action states that "there is insufficient written description about the structure associated with function of any isolated antibody which specifically binds to" the recited "variants" and "fragments" of SEQ ID NO:1, and asserts that "the disclosure fails to provide a representative number of species to describe the genus" (Office Action, August 13, 2002; page 8). The Office Action further asserts that the use of

the terms "having" and "comprising" "expands the polypeptide fragment to include additional amino acid residues at either or both ends to which the antibody binds" (Office Action, page 8). This rejection is traversed.

With respect to the use of the terms "having" and "comprising," the specification provides an adequate written description of antibodies which specifically bind to the recited polypeptides "having" and "comprising" variants and fragments of SEQ ID NO:1.

Nevertheless, to expedite prosecution, claim 11 has been amended such that it recites antibodies which bind to an epitope of SEQ ID NO:1, which bind to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1, or which bind to an epitope of a fragment of a polypeptide consisting of SEQ ID NO:1. Support for these amendments can be found in the specification at, for example, page 8, lines 1-6. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include antibodies which bind to epitopes other than those recited in the claims. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claims, as amended, recite patentable subject matter.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other

> physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" and "fragments" of SEQ ID NO:1.

The subject matter encompassed by claims 11, 31-32, 34, 36-43, and 58 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 11 recites polypeptides "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity." Furthermore, the "fragment" language of independent claim 11 recites polypeptides "comprising a fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment has CoA dehydrogenase activity," and polypeptides "comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing and Figures 1A, 1B, 1C, 1D, and 2. Variants of SEQ ID NO:1 are described in the specification at, for example, page 3, lines 5-6; page 6, line 18 to page 7, line 4; page 7, lines 9-12; page 14, lines 12-19; and page 15, lines 15-18; and fragments of SEQ ID NO:1 are described at, for example, page 3, lines 2-4; page 7, lines 5-9; page 8, lines 15-18; page 28, lines 21-25; and page 51, lines 7-16. In addition, a specific assay to measure CoA dehydrogenase activity is disclosed in the specification at, for example, page 50, line 21 to page 51, line 2.

One of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. It would also be routine to determine whether such a variant had CoA dehydrogenase activity, using the disclosed CoA dehydrogenase assay. Accordingly, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1.

One of ordinary skill in the art would recognize polypeptide sequences which are fragments of SEQ ID NO:1. The amino acid sequence of SEQ ID NO:1 provides the necessary framework for the recited fragments - to recite every possible fragment would needlessly clutter the application. It would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had CoA dehydrogenase activity, using the disclosed CoA dehydrogenase assay. Likewise, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had immunogenic activity, based on the methods recited in the specification at, for example, page 8, lines 15-18; page 28, line 6 to page 30, line 1; and page 51, lines 4-19. Accordingly, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide fragments of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 11

recites chemical structure to define the claimed genus:

> 11. An isolated antibody selected from the group consisting of:
> a) an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein the antibody specifically binds to an epitope of a polypeptide of SEQ ID NO:1,
> b) an antibody which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity, and wherein the antibody specifically binds to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1,
> c) an antibody which specifically binds to a fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment has CoA dehydrogenase activity, and wherein the antibody specifically binds to an epitope of the fragment, and
> d) an antibody which specifically binds to an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polypeptides which are short-chain dehydrogenases including polypeptides which are short-chain dehydrogenases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as short-chain dehydrogenases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 313 amino acid residues). This variation is far less than that of all potential short-chain dehydrogenases related to SEQ ID NO:1; i.e., those short-chain dehydrogenases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of February 5, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies which specifically bind the recited polypeptide variants and fragments at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide "variants" and "fragments," and this rejection should be withdrawn.

V. Rejection under 35 U.S.C. § 102(b)

Claims 11 and 36-37 were rejected under 35 U.S.C. § 102(b) because the recited antibodies are allegedly anticipated by Verwoert et al. (J. Bacteriol. (1992) 174:2851-2857). This rejection is traversed.

The Office Action asserts that "Verwoert *et al* teach an antibody that binds to a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues identical to the claimed SEQ ID NO:1" (Office Action, August 13, 2002; § 10 at page 9). This is incorrect. While it may be true that the antibodies taught by Verwoert et al. could possibly bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof, this binding would not be **specific**. For example, the specification discloses that:

> Various immunoassays may be used for screening to identify antibodies having the **desired specificity**. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between HSCD and its **specific antibody**. (Specification, page 29, lines 24-28; emphasis added)

The antibodies recited by the claims **specifically** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

For at least the above reasons, withdrawal of this rejection is requested.

VI. Rejection of claims 11, 31, 42, and 43 under 35 U.S.C. § 103(a)

Claims 11, 31, 42, and 43 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies are allegedly obvious over Verwoert et al. (J. Bacteriol. (1992) 174:2851-2857) in view of Queen et al. (U.S. Patent No. 6,180,370 B1). This rejection is traversed.

This rejection is based on the allegation that the antibodies taught by Verwoert et al. are within the scope of the claimed antibodies. As discussed above in § V, the claims recite antibodies which **specifically** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to

polypeptides other than those recited in the claims.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al., the Patent Office has not convincingly shown how the teachings of Verwoert et al. and/or Queen et al. could be modified in order to arrive at the claimed subject matter. Therefore, the Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of this rejection is requested.

VII. Rejection of claims 11 and 31 under 35 U.S.C. § 103(a)

Claims 11 and 31 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies are allegedly obvious over Verwoert et al. (J. Bacteriol. (1992) 174:2851-2857) in view of Ladner et al. (U.S. Patent No. 4.946,778). This rejection is traversed.

This rejection is based on the allegation that the antibodies taught by Verwoert et al. are within the scope of the claimed antibodies. As discussed above in § V, the claims recite antibodies which **specifically** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al., the Patent Office has not convincingly shown how the teachings of Verwoert et al. and/or Ladner et al. could be modified in order to arrive at the claimed subject matter. Therefore, the

Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of this rejection is requested.

VIII. Rejection of claims 11, 31-32, and 34 under 35 U.S.C. § 103(a)

Claims 11, 31-32, and 34 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies are allegedly obvious over Verwoert et al. (J. Bacteriol. (1992) 174:2851-2857) in view of Harlow et al. (in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 319-356 and 626-629). This rejection is traversed.

This rejection is based on the allegation that the antibodies taught by Verwoert et al. are within the scope of the claimed antibodies. As discussed above in § V, the claims recite antibodies which **specifically** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al., the Patent Office has not convincingly shown how the teachings of Verwoert et al. and/or Harlow et al. (pages 319-356 and 626-629) could be modified in order to arrive at the claimed subject matter. Therefore, the Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of this rejection is requested.

IX. Rejection of claims 11 and 38-41 under 35 U.S.C. § 103(a)

Claims 11 and 38-41 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies are allegedly obvious over Verwoert et al. (J. Bacteriol. (1992) 174:2851-2857) in view of Harlow et

al. (in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 139-149). This rejection is traversed.

This rejection is based on the allegation that the antibodies taught by Verwoert et al. are within the scope of the claimed antibodies. As discussed above in § V, the claims recite antibodies which **specifically** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02. Since the claim language distinguishes the recited antibodies from the antibodies taught by Verwoert et al., the Patent Office has not convincingly shown how the teachings of Verwoert et al. and/or Harlow et al. (pages 139-149) could be modified in order to arrive at the claimed subject matter. Therefore, the Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of this rejection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Please charge Deposit Account No. **09-0108** in the amount of $110 for a one-month extension of time, as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: Nov. 15, 2002

Terence P. Lo, Ph.D.
Limited Recognition (37 C.F.R. § 10.9(b)) attached
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 11 has been amended as follows:

11. (Twice Amended) An isolated antibody [which specifically binds to a polypeptide] selected from the group consisting of:

a) an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein the antibody specifically binds to an epitope of a polypeptide of SEQ ID NO:1,

b) an antibody which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity, and wherein the antibody specifically binds to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1,

c) an antibody which specifically binds to a polypeptide comprising a fragment of a polypeptide [having] consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment has CoA dehydrogenase activity, and wherein the antibody specifically binds to an epitope of the fragment, and

d) an antibody which specifically binds to a polypeptide comprising an immunogenic fragment of a polypeptide [having] consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment.